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EXAMINER
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HYUN, PAUL SANG HWA

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1797

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ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

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### **DETAILED ACTION**

The amendment filed by Applicant on March 24, 2010 has been acknowledged. Claims 1-19 and 29-53 are currently pending. Applicant amended claims 30-33, 35-38 and added new claims 39-53.

The IDS filed by Applicant on March 24, 2010 has been acknowledged.

Despite Applicant's arguments, the rejection of claims 1-19, 29, 32, 34 and 37 are maintained.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims **30, 31, 35, 36, 48 and 49** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claims 30, 31, 35, 36, 48 and 49 recite a program comprising an instruction to resume reagent delivery to wells if one or more criteria are met. The originally filed Specification does not provide support for the amendment. The Specification discloses that the invention comprises a program that decides whether to continue synthesis based on one or more criteria. However, the Specification does not

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provide support for a program that resumes reactions in wells where failure was previously detected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **33, 38 and 51** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33, 38 and 51 recite an analyzer program that indicates a failure if the difference between two values (i.e. value expected and measured value) comprises an increasingly negative slope. It is unclear how a subtraction of two values can yield a slope. Slope requires data gathered over a period of time. Based on the disclosure of the Specification, it appears that Applicant intended to recite 'an analyzer program that indicates a failure if the change in difference between the value expected and the specific value over a period of time comprises an increasingly negative slope'.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims **1-3, 6-10, 13-16, 18, 19, 29, 32, 34, 37, 39-43, 46, 47, 52 and 53** are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch (US 6,083,763) in view of VanBrunt et al. (US 2004/0067164 A1).

Balch discloses an automated molecular analyzer (see Figs. 1 and 9). The analyzer can be used to conduct nucleotide synthesis (e.g. PCR) (see lines 25-45, col.

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21). The analyzer comprises a microplate comprising an array of wells (see lines 40-50, col. 4), a dispensing system for delivering reagents to the wells of the microplate (see lines 60-63, col. 5 and claim 1), a light source (e.g. UV lamp, laser) pivotally mounted on one side of a viewing window for exciting the contents of the wells (see lines 35-40, col. 28), a CCD camera positioned beneath the viewing window to obtain images of the wells (see lines 14-50, col. 4), and a software program for providing automated filtering, thresholding, labeling, statistical analysis and quantitative graphical display of each well within seconds (see lines 25-34, col. 6). Because the software program produces quantitative graphical display of each well and performs thresholding, it is evident that the software program determines a value associated with the extent of the reaction in each well and it is capable of monitoring the progress of the reaction in each well (see also lines 42-50, col. 35, which discloses that the CCD is capable of monitoring hybridization reactions during PCR). The analyzer disclosed by Balch differs from the claimed invention in that Balch does not disclose a dispenser that is configured to discontinue dispensing of reagents to wells where a reaction is not taking place. In addition, Balch does not disclose an aspiration means.

VanBrunt et al. disclose an apparatus for conducting automated assay. The apparatus comprises an array of fluid vessels, a dispensing system that can also aspirate fluids (see [0064]), an optical detector (see [0069]) for monitoring the progress of reactions occurring in the fluid vessels, and a system for processing the output of the detector to determine the subsequent processing step (see Abstract and [0095]). The apparatus is configured such that in the event that the detector does not detect a

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reaction occurring in a vessel, further processing of that fluid vessel is aborted (see [0095]). In light of the disclosure of VanBrunt et al., it would have been obvious to one of ordinary skill in the art to configure the dispenser disclosed by Balch such that it stops delivering reagents to wells that are not exhibiting any reactions. Such modification would save time and cost. It also would have been obvious to one of ordinary skill in the art to provide the Balch system with an aspirating means as taught by VanBrunt et al. so that fluids from the vessels can be transferred to another vessel.

With respect to claim 10, although Balch does not explicitly disclose that the analyzer can write the data derived by the software program to a data storage location, it would have been obvious, if not apparent, to enable the analyzer to do so to enable one to access the data at a later time. It is well known in the art that computers are capable of saving data to a storage device.

Claims **4, 5 and 17** are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of VanBrunt et al. as applied to claims 1-3, 6-10, 13-16, 18, 19, 29, 32, 34, 37, 39-43, 46, 47, 52 and 53 above, and further in view of Vo Dinh et al. (US 6,448,064 B1).

Neither Balch nor VanBrunt et al. disclose the use of LED arrays to excite the sample.

Vo Dinh et al. disclose a biochip for conducting reactions. The biochip comprises an array of reaction sites 143 and a plurality of LED arrays 144, each LED array configured to excite the sample of one reaction site (see Fig. 3 and Example 5, col. 16).

In light of the disclosure of Vo Dinh et al., it would have been obvious to use LEDs to excite the sample disclosed by Balch since LEDs are common and cheaper than laser. It also would have been obvious to provide a light source for each reaction site of the modified Balch analyzer. The use of a plurality of light sources would increase efficiency.

Claim **11** is rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of VanBrunt et al. as applied to claims 1-3, 6-10, 13-16, 18, 19, 29, 32, 34, 37, 39-43, 46, 47, 52 and 53 above, and further in view of Eyster et al. (US 2003/0207441 A1).

Neither Balch nor VanBrunt et al. disclose a computer system that generates a warning message based on the extent of the reaction occurring within the reaction site of an array.

Eyster et al. disclose an apparatus for measuring the concentration of an analyte of interest. The apparatus comprises an array of sample, a light source for inducing a signal from the array of sample, a CCD camera for producing an image of the signal (see [0077]), and a means for displaying a message if the measurement values derived from the wells deviate from a control value (see [0102]). In light of the disclosure of Eyster et al., it would have been obvious to one of ordinary skill in the art to provide the modified Balch analyzer with a means that can generate a message if measurement values derived from the wells deviate from a control value so that the user can determine the source of the deviation.

Claim **12** is rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of VanBrunt et al. as applied to claims 1-3, 6-10, 13-16, 18, 19, 29, 32, 34, 37, 39-43, 46, 47, 52 and 53 above, and further in view of Dower et al. (US 5,639,603).

Neither Balch nor VanBrunt et al. disclose a centrifuge rotor associated with the liquid removing device.

Dower et al. disclose an automated apparatus for conducting synthesis reactions in a microplate wherein the apparatus comprises an aspirator for removing fluid from the wells of the microplate. The apparatus can further comprise a centrifuge for separating the contents of a reaction vessel prior to aspirating those contents (see lines 42-59, col. 42). In light of the disclosure of Dower et al., it would have been obvious to one of ordinary skill in the art to provide a centrifuge to the modified Balch analyzer so that the contents of the wells of the microplate can be separated prior to removing the content of interest from the wells.

Claims **1-4, 6-8, 29, 32, 39-43, 46, 47, 52 and 53** are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Hartwich et al. (WO 01/69210 A1).

As discussed above, Balch discloses an automated molecular analyzer (see Figs. 1 and 9). The analyzer disclosed by Balch differs from the claimed invention in that Balch does not disclose a dispenser that is configured to discontinue dispensing of reagents to wells where a reaction is not taking place.

Hartwich et al. disclose an automated system for carrying out reactions in an array format (e.g. microplate). The system comprises a supply system (e.g. pipette),



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and a scanning system for detecting the existence of a reaction in the wells of the array. If the scanning system does not detect a reaction in a well belonging to a group of wells designated for conducting a specific reaction, further scanning of the rest of the wells belonging to that group is discontinued to optimize efficiency and cost. In light of the disclosure of Hartwich et al., it would have been obvious to one ordinary skill in the art to configure the dispenser disclosed by Balch such that it stops delivering reagents to wells that are not exhibiting any reactions. Such modification would save time and cost.

With respect to claim 4, Balch does not disclose the use of an array of LEDs as the light source. However, Hartwich et al. disclose the use of an array of LEDs to excite samples in the wells (see claim 4). In light of the disclosure, it would have been obvious to use an array of LEDs as the light source in the system disclosed by Balch since diodes are much cheaper than laser.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Hartwich et al. as applied to claims 1-4, 6-8, 29, 32, 39-43, 46, 47, 52 and 53, and further in view of Vo Dinh et al.

Neither Balch nor Hartwich et al. disclose the use of more than one LED array to excite the sample.

Vo Dinh et al. disclose a biochip for conducting reactions. The biochip comprises an array of reaction sites 143 and a plurality of LED arrays 144, each LED array configured to excite the sample of one reaction site (see Fig. 3 and Example 5, col. 16). In light of the disclosure of Vo Dinh et al., it would have been obvious to provide a light

source for each reaction site of the modified Balch analyzer. The use of a plurality of light sources would increase efficiency and minimize cost.

Claims **9, 10, 13-16, 18, 19, 34 and 37** are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Hartwich et al. and Becker et al. (US 7,625,061 B1).

As discussed above, Balch discloses an automated molecular analyzer. The analyzer disclosed by Balch differs from the claimed invention in that Balch does not disclose a dispenser that is configured to discontinue dispensing of reagents to wells where reaction is not taking place. In addition, Balch does not disclose an aspiration means.

With respect to the dispenser that is configured to discontinue dispensing of reagents to wells where a reaction is not taking place, Hartwich et al. disclose such a device as discussed above. In light of the disclosure of Hartwich et al., it would have been obvious to one ordinary skill in the art to configure the dispenser disclosed by Balch such that it stops delivering reagents to wells that are not exhibiting any reactions. Such modification would save time and cost.

With respect to the aspiration means, Beck et al. disclose an automated system for performing polynucleotide synthesis reactions. The system comprises a microplate (see line 55, col. 15), a CCD for obtaining images of the wells of the microplate, a dispensing system, and a device for removing liquids from the wells of the microplate (see lines 36-56, col. 23). The device can transfer the aspirated fluid to another target

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site or a waste chamber. In light of the disclosure of Becker et al., it would have been obvious to one of ordinary skill in the art to provide the Balch system with a device that can remove fluids from the wells of the microplate to another well or to dispose of it.

With respect to claim 10, although Balch does not explicitly disclose that the analyzer can write the data derived by the software program to a data storage location, it would have been obvious, if not apparent, to enable the analyzer to do so to enable one to access the data at a later time. It is well known in the art that computers are capable of saving data to a storage device.

With respect to claim 16, Balch does not disclose the use of an array of LEDs as the light source. However, Hartwich et al. disclose the use of an array of LEDs to excite samples in the wells (see claim 4). In light of the disclosure, it would have been obvious to use an array of LEDs as the light source in the system disclosed by Balch since diodes are much cheaper than laser.

Claim **11** is rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Hartwich et al. and Becker et al. as applied to claims 9, 10, 13-16, 18, 19, 34 and 37, and further in view of Eyster et al.

None of Balch, Hartwich et al. and Becker disclose a computer system that generates a warning message based on the extent of the reaction occurring within the reaction site of an array.

Eyster et al. disclose an apparatus for measuring the concentration of an analyte of interest. The apparatus comprises an array of sample, a light source for inducing a

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signal from the array of sample, a CCD camera for producing an image of the signal (see [0077]), and a means for displaying a message if the measurement values derived from the wells deviate from a control value (see [0102]). In light of the disclosure of Eyster et al., it would have been obvious to one of ordinary skill in the art to provide the modified Balch analyzer with a means that can generate a message if measurement values derived from the wells deviate from a control value so that the user can determine the source of the deviation, whether it be an error in the CCD or the protocol of the experiment.

Claim **12** is rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Hartwich et al. Becker et al. as applied to claims 9, 10, 13-16, 18, 19, 34 and 37, and further in view of Dower et al.

None of Balch, Hartwich et al. and Becker et al. disclose a centrifuge rotor associated with the liquid removing device.

Dower et al. disclose an automated apparatus for conducting synthesis reactions in a microplate wherein the apparatus comprises an aspirator for removing fluid from the wells of the microplate. The apparatus can further comprise a centrifuge for separating the contents of a reaction vessel prior to aspirating those contents (see lines 42-59, col. 42). In light of the disclosure of Dower et al., it would have been obvious to one of ordinary skill in the art to provide a centrifuge to the modified Balch analyzer so that the contents of the wells of the microplate can be separated prior to removing fluid from the wells.

Claim **17** is rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Hartwich et al. and Becker as applied to claims 9, 10, 13-16, 18, 19, 34 and 37, and further in view of Vo Dinh et al.

None of Balch, Hartwich et al. and Becker disclose the use of more than one LED array to excite the sample.

Vo Dinh et al. disclose a biochip for conducting reactions. The biochip comprises an array of reaction sites 143 and a plurality of LED arrays 144, each LED array configured to excite the sample of one reaction site (see Fig. 3 and Example 5, col. 16). In light of the disclosure of Vo Dinh et al., it would have been obvious to provide a light source for each reaction site of the modified Balch analyzer. The use of a plurality of light sources would increase efficiency and minimize cost.

Claims **39-47, 50, 52 and 53** are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch in view of Davies et al. (US 2003/0143591 A1).

As described above, Balch discloses an automated molecular analyzer (see Figs. 1 and 9). The analyzer can be used to conduct nucleotide synthesis, including PCR (see lines 42-50, col. 35). The analyzer disclosed by Balch differs from the claimed invention in that Balch does not disclose a dispenser that is configured to discontinue dispensing of reagents to wells where reaction is not taking place.

Davies et al. disclose a system for conducting PCR (see Abstract). The system is capable of monitoring the progress of reactions in real time. The system is configured to

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detect the existence of failed reactions based on production of amplicons as well as the existence of inefficient reactions based on the type of amplicons produced (see [0187]).

The system is programmed to stop the reaction at any given cycle based on these measurements (see [0187]). The reference discloses that real time monitoring saves materials. In one embodiment, the system monitors the progress of reactions by optically measuring the amount of dimethyltrityl groups (DMT) released (see claim 25). In light of the disclosure of Davies et al., it would have been obvious to one of ordinary skill in the art to provide the analyzer disclosed by Balch with a program that monitors the progress of PCR reactions in real time based on DMT concentration and cease processing of test sites exhibiting failed or inefficient reactions.

### ***Response to Arguments***

Applicant's arguments with respect to the claims have been fully considered but they are not persuasive.

1) Applicant argues that the claims are patentable over the disclosure of Balch and VanBrunt et al. because there is no motivation to combine the references. Specifically, Applicant argues that VanBrunt et al. disclose a liquid dispensing device that is programmed to maintain a proper fluid level in reaction vessels. Applicant argues that there is no motivation to apply this feature to the invention disclosed by Balch. This argument is not persuasive. As indicated in the rejection above, VanBrunt et al. was relied upon for its disclosure of the concept of using an optical detector to determine whether a reaction is taking place inside a reaction vessel and subsequently decide whether to abort further processing of the reaction vessel. Although the specific

algorithm used by VanBrunt et al. to determine the existence of a reaction may not be applicable to the invention disclosed by Balch, the general concept of using an optical detector and an analyzer to assess the progress of reactions taking place inside a reaction vessel to decide whether to abort further processing of said vessel is applicable to the invention disclosed by Balch. Because the claims do not specify the algorithm for determining whether to discontinue reagent delivery to a reaction well, there is sufficient motivation to apply the broad concept disclosed by VanBrunt et al. to the invention disclosed by Balch. For the foregoing reason, Applicant's argument that there is no motivation to combine the disclosure of Balch and VanBrunt et al. is not persuasive.

2) Applicant argues that the claims are patentable over the disclosure of Balch and VanBrunt et al. because the references do not disclose all the elements recited in the claims. Specifically, Applicant argues that the claims recite an analyzer that determines whether a difference between a value expected if a chemical reaction is successful and the measured value exceeds a threshold value. This argument is not persuasive. VanBrunt et al. disclose an optical detector that is capable of detecting the presence of no reaction in a well after comparing a measured value associated with the well to a reference value (see [0095] and Abstract). The Examiner maintains the position that VanBrunt et al. properly disclose the claimed detector and analyzer. The fact that the detector disclosed by VanBrunt et al. utilizes an algorithm that differs from the algorithm pondered by Applicant is not significant. The claims merely require an analyzer that determines whether a reaction is successful, and the analyzer disclosed by VanBrunt accomplishes that. For the foregoing reason, Applicant's

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argument that the claims are patentable over the disclosure of Balch and VanBrunt et al. because the references do not disclose all the elements recited in the claims is not persuasive.

3) Applicant argues that the claims are patentable over the disclosure of Balch and Hartwich et al. because there is no motivation to combine the references. Specifically, Applicant argues that the disclosure of Hartwich et al. does not pertain to an analyzer that discontinues reagent delivery to a reaction site where no reaction is taking place. This argument is not persuasive. Hartwich et al. disclose a system comprising an optical detector and an analyzer that determines whether a reaction is taking place in a test site of an array. If no reaction is detected at a particular test site, the analysis of other test sites involved in similar reactions is discarded to save time and cost. While the disclosure of Hartwich et al. does not pertain to reagent dispensing, the Examiner maintains the position that the concept taught by Hartwich et al. is broadly applicable to the disclosure of Balch, which also pertains to array processing of samples. In other words, while the disclosure of Hartwich et al. is limited to an analyzer that discards optical measurements when a failed reaction is detected, it would have been obvious to one of ordinary skill in the art to discard all sample processing steps that proceed the determination made by the analyzer, including reagent dispensing. In this instance, the system disclosed by Balch is configured to conduct nucleotide synthesis, which involves reaction cycles. That said, in light of the disclosure of Hartwich et al., it would have been obvious to one of ordinary skill in the art to configure the Balch apparatus to monitor the progress of the reaction sites after each reaction



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cycle, and determine whether to cease further processing of the reaction sites based on the presence of reactions at the reaction sites.

For the foregoing reasons, the rejections are maintained.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **PAUL S. HYUN** whose telephone number is (571)272-8559. The examiner can normally be reached on Monday-Friday 8AM-4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571)-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner, Art Unit 1797

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